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EXAMINER	
WILDER, CYNTHIA B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,951	TAO ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/2008 and 11/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-27, drawn to a method for optimizing multiplex PCR primers.

Group II, claim(s) 28-29, drawn to a composition and kit.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The claims are not linked by the same or corresponding special technical features because the broadest first named invention, namely, the reagent kit as described in Group II is not "special" and does not provide a contribution over the prior art (See Heath et al, Journal of Medical Genetics, vol. 37, pages 272-280, 2000). Additionally, the special technical feature is not special because the different inventions have different structural properties, different function and/or use. For example, the method of Group I is drawn to multiplex amplification reactions for comparing amplified products to identify optimized multiplex PCR primers. Searching the inventions of Groups I-II would constitute a serious search burden to the Examiner because the searches of the inventions of Groups I-II are not coextensive because each of the inventions of Group I-II can function irrespective of the other invention. For example, the composition comprising a plurality of different concentrations of specific and universal oligonucleotides can be used in methods of universal labeling of DNA amplification products or in PCR-ELISA assays or in forensic applications for species identification.

2. During a telephone conversation with Mr. Peng Cheng on April 14, 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-27. Affirmation of this election must be made by applicant in replying to this

Office action. Claims 28-29 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the

above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Specification

5. The disclosure is objected to because of the following informalities: The specification is objected to at pages 13 for the use of symbols in lines 14, 18 and 20, at page 14 in Table 1 and at page 15, line 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2 and 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 2 is indefinite at "suitable conditions" because the terms have not been defined in the specification or claims as it cannot be determine what conditions are most appropriate for the formation of hairpin structures.

(b) Claim 11 lacks proper antecedent basis for "the nearest neighbor method" because the claim 1 from which the claim depends to not recite or identify "a neighbor

method". Accordingly, it cannot be determined what method applicant is making reference to.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 3-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al (Journal of Medical Genetics, vol. 37, pages 272-280, 2000) in view Shuber (Genome Research, citation made of record) of Elnifro et al (Clinical Microbiology Reviews, citation made of record on IDS filed 11/10/2006). Regarding claims 1, 3-18, and 21, Heath et al teach a method comprising providing a plurality of 5' and 3' specific primers each of said specific primers comprising a specific sequence complementary to its target sequence to be amplified to amplified and a common sequence, providing a 5'

and 3' universal primer said 5' universal primer being complementary to said common sequence of said 5' specific primer and said 3' universal primer complementary to said common sequence of said 3' specific primer primers, conducting as plurality of multiplex PCR on a plurality of target sequences in the presence of said plurality of 5' and 3' specific primer and said 5' and 3' universal primers, wherein in each of said PCRS, the concentration of the said 5' and 3' universal primers is equal to the concentration of said 5' and 3' specific primers and the concentration of said 5' and 3' primers in different PCRs are different and assessing PCR products obtained via electrophoresis (pages 273-274 (Table 1 and Figure 1). Heath et al teach that the method is useful because comparable yields of the individual coamplified products are obtained with the use of universal primer in a qualitative PCR based method. (Page 273, col. 2, first full paragraph).

Heath et al do not teach expressly wherein the PCR products of said different PCRS are compared to identify optimized multiplex PCR primers.

MPEP states " "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Furthermore, the prior art recognizes the need for improving optimization of multiplex reaction conditions and primers. For example, Shuber et al, as cited by Heath et al, teach a method for multiplex PCRs wherein the each primer contains a 3' region complementary to sequence specific recognition sites and 5' region made up of an unrelated 20 nucleotide sequence and a universal primer sequence which contain

the 20 nucleotide sequence of the 5' end of the sequence specific primer (see abstract and page 40, "Primer Design"). In recognizing the need for improving optimization of multiplex reaction conditions and primers, Shuber et al teach that

> "[i]n general a number of considerations and optimization steps are involved in developing a robust and efficient multiplex PCR. For example, multiplexing is frequently complicated by artifacts such as the amplification of spurious products resulting from annealing of the primers to nonspecific sequences. Typically, primers should be designed so that their predicted melting temperatures are similar to those of the other primers used in the multiplex reaction. Although the annealing temperatures and primer concentrations may be calculated to some degree, conditions generally must be defined empirically in multiplex reactions. In addition, as primer sets are added to the multiplex PCR, reaction components (e.g., Mg^{2*}, dNTP, polymerase) and cycling conditions (e.g., annealing temperature, extension time, hot start) must also be adjusted. Therefore, complete optimization of the reaction conditions for multiplex PCR can become labor intensive and time conditions, development of new diagnostic tests can become very costly.(page 488).

To improve optimization conditions, Shuber et al teach that simple adjustments of the individual primer concentration with no additional modification of either the reaction components or annealing temperatures can result in highly specific and efficient amplification of target sequence easily and reproducibly (page 492, col. 2, first paragraph under "Discussion").

Elnifro et al supports the teachings of Shuber et al and recognizes the need for improved optimization conditions. Elnifro et al teach that "optimization of multiplex PCRs can prove difficult. Elnifro et al teach

"[A] stepwise matrix-style approach may be followed, i.e., a number of optimal primer pairs are combined and the combination giving the best results (based on

comparisons) is then chosen to be optimized or evaluated in a multiplex PCR format (page 567, col. 2, first five lines of the last paragraph).

It would have been obvious to one having ordinary skill in the art to have compared the PCR products of the multiplex amplification reactions of Heath et al to identify optimal PCR primers as suggested by Elnifro et al. One of ordinary skill in the art at the time of the claimed invention would have been motivated to identify optimal multiplex PCR primers for the predictable results of improving specificity and efficiency of amplification of target sequences in an easy and reproducible manner without additional modification of reaction components or annealing temperatures as suggested by Shuber et al.

Regarding claim 17-20, the claims merely recite a plethora of conventional nucleic acid manipulation reagents and methodologies, as well as well as routine optimization or reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards patentability. Thus, one of ordinary skill in the art would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations and/or expanded applications. For example, Heath et al teach wherein the PCR product is analyzed via polyacrylamide electrophoresis (page 274). Shuber et al teach wherein agarose gel electrophoresis is used to analyze the PCR product page 490). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

Regarding claim 22, Heath et al teach wherein the target sequence is human origin (page 273, col. 2). Elnifro et al teach wherein the target is viral (see Table 1, page 560).

Regarding claim 23, Elnifro et al teach wherein the target sequences are derived from viruses that are associated with upper and lower respiratory infections (see Table 2). The virus SARS-CoV is within the scope of the teachings of Elnifro et al as it is a respiratory syndrome.

11. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al in view of Shuber et al in view of Elnifro et al as previously described above and further in view of Nazarenko et al (Nucleic acids Research, vol. 30, page e37 1-7). Regarding claim 2, Heath et al in view of Shuber et al in view of Elnifro et al teach a method of performing multiplex PCR reactions using by improving the optimal PCR primer conditions and reaction conditions as previously described above.

The references do not teach wherein the reaction is performed in the presence of a specific primer which forms a hairpin structure.

Nazarenko et al provide a multiplex PCR reaction, similar to that of Heath et al wherein primers which form hairpin structures are used. Nazarenko et al teach that the use of hairpin primers improves the specificity of PCR by reducing the formation of primer-dimer artifacts in the absence of target. Nazarenko further recognize the need to optimize PCR and primer designs. Nazarenko et al teach that "despite efforts to optimize PCR and primer designs, they find that some primer pairs still form artifacts",

which results in primer-dimer formation causing false negative results or inaccurate quantitation (page 6, third paragraph from bottom of col. 2).

One of ordinary skill in the art at the time of the claimed invention would have been motivated to have incorporated a primer that forms a hairpin structure as taught by Nazarenko et al in the multiplex amplification reaction of Heath et al in view of Shuber and Elnifro et al for the predictable benefit of reducing primer-dimer formation, thereby increasing the specificity and reliability of the multiplex amplification reaction as suggested by Nazarenko. Such use of a hairpin structure primer in the multiplex reaction would optimize the multiplex PCR conditions and primer designs.

12. Claims 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al in view of Shuber et al in view of Elnifro et al as previously described above and further in view of Dovas et al (Journal of Virological Methods, vol. 109, pages 217-226, available online March 2003). Regarding claims 24-27, , Heath et al in view of Shuber et al in view of Elnifro et al teach a method of performing multiplex PCR reactions using by improving the optimal PCR primer conditions and reaction conditions as previously described above. The references teaches wherein quantitative multiplex PCR or convention multiplex PCR is used but do not teach wherein multiplex one-step RT PCR or multiplex nested PCR is used. However, the uses of these known techniques are merely a manipulation of reagents and methodologies, as well as routine optimization of reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards

patentability. Thus, one of ordinary skill in the art would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations and/or expanded applications. For example, Dovas et al teach the use of a one tube RT-PCR reaction and nested PCR reaction in a multiplex format (see for example Figure 2). Dovas et al teach that use of these techniques allowed the reliable detection of multiple viral species from three different genera allowing simple, fast and a cost effective testing of a large number of samples (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods using different combination of multiplex amplification reaction, such as those taught by Dovas in the method of Heath et al in view of Shuber et al and Elnifro et al for the predictable benefit of increasing the ability to analyze a large number of diverse sample in a reliable, simple, fast and cost-effective manner as suggested by Dovas et al.

Conclusion

13. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Patent Examiner
Art Unit 1637

4/23/2008